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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/960,244	09/21/2001	Tony W. Ho	2831.2003-000	4326
21005	7590	03/24/2004	EXAMINER	
HAMILTON, BROOK, SMITH & REYNOLDS, P.C. 530 VIRGINIA ROAD P.O. BOX 9133 CONCORD, MA 01742-9133			AFREMOVA, VERA	
			ART UNIT	PAPER NUMBER
			1651	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/960,244

Applicant(s)

HO ET AL.

Examiner

Vera Afremova

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 24 December 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-14, 19-21, 23 and 25-93 is/are pending in the application.
- 4a) Of the above claim(s) 1-13 and 27-93 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 14, 19-21, 23 and 25 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                                   | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)               | Paper No(s)/Mail Date. _____  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                                    |

## **DETAILED ACTION**

### ***Status of claims***

Claims 14, 19-21, 23 25 and 26 as amended (12/24/2003) are pending and under examination.

Claims 15-18, 22 and 24 were canceled by applicants (12/24/2003). Claims 1-13 and 27-93 were withdrawn from consideration. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

### ***Claim Rejections - 35 USC § 102***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim rejection under 35 U.S.C. 102(b) as being anticipated by Ross et al. has been withdrawn because the reference does not teach cells derived from bone marrow as required by the presently amended claims.

Claim rejection under 35 U.S.C. 102(e) as being anticipated by US 2002/0168765 or under 35 U.S.C. 102(a) as being anticipated by WO 01/34167 in the light of evidence by Cooper et al. and US 5,837,539 has been withdrawn the cited patent do not disclose isolated cell population isolated wherein 91% of cells co-express CD49c and CD90.

Claim rejection under 35 U.S.C. 102(a) as being anticipated by W0 01/11011 in the light of evidence by Cooper et al. and US 5,837,539 has been withdrawn the cited patent do not disclose isolated cell population isolated wherein 91% of cells co-express CD49c and CD90.

***Claim Rejections - 35 USC § 103***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 14, 19, 20, 23, 24 and 26 as amended are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2002/0168765, WO 01/34167 and WO 01/11011 in the light of evidence by US 5,837,539 and Colter et al. {IDS –AW}.

Claims as amended are drawn to a cell population isolated from bone marrow wherein 91% of cells co-expresses CD49c and CD90 and wherein the cell population has doubling time of less than about 30 hours. Some claims are further drawn to the cells which do not express CD34 and CD45 but express additional markers including IL-6, MCP-I. Some claims are further drawn to the cells that are capable to differentiate into various cell phenotypes including osteoblasts, chondrocytes and neuronal cells types. Some claims are further drawn to the cells that are human cells.

The cited patents US 2002/0168765, WO 01/34167 and WO 01/11011 are relied upon as explained in the prior office action and repeated herein as applied to the amended claims.

The cited patents US 2002/0168765, WO 01/34167 and WO 01/11011 disclose cell populations isolated from human bone marrow wherein the cells retain capability to differentiate into various cell phenotypes including osteoblasts, chondrocytes and neuronal cells types. The cells co-express CD49 (alpha integrin) and CD90 but they do not express CD34 and CD45.

For example: see WO 01/34167 at page 14, lines 2-22; Fig. 26 and page 16, lines 17-20. The disclosure of US 2002/0168765 is the same as in WO 01/34167. For example: see WO 01/11011 at page 8, lines 24-30 and at page 9, lines 7-10.

The cited patents US 2002/0168765 and WO 01/34167 clearly indicate expression of CD49 but they are silent about specific type of alpha integrin such as CD49c. However, WO 01/11011 discloses expression of the specific CD49 such as CD49c (page 26, line 14). In addition, US 5,837,539 is relied upon to demonstrate the inherent presence of all the CD49 type adhesion structures including integrins alpha 1 (CD49a), alpha 2 (CD49b), alpha 3 (CD49c) and alpha 5 (CD49e) on mesenchymal stem cells derived from bone marrow (See table 5, at col. 39-40). The cited patent US 5,837,539 also teaches that human mesenchymal stem cells derived from bone marrow express high levels of IL-6 in basic and regular culture media (col. 40, line 30). The mesenchymal stem cells derived from bone marrow express additional markers including MCP1, for example: see WO 01/11011 at page 26, line 12.

The cited patents US 2002/0168765, WO 01/34167 and WO 01/11011 teach that the isolated cell populations are rapidly proliferating. For example: WO 01/34167 demonstrates on the figure 22 that the doubling time is less than 30 hours. In addition, the IDS reference by Colter et al. is relied to demonstrate that the same population of mesenchymal cells isolated from bone marrow has doubling time of about 12 hours (page 3214, col. 1, last 3 lines). Thus, although the cited patents might be silent or they might not indicate the same growth rate as required by the present claims, the same cell population of mesenchymal cells, that is isolated from bone marrow and that is co-expresses CD49 and CD90, is capable to exhibit the growth rate as required by the claims.

The cited patents US 2002/0168765, WO 01/34167 and WO 01/11011 are either silent about the particular amount of cells that co-express CD49 and CD90 or they do not teach that the isolated cell product contains 91% of cells co-expressing CD49 and CD90.

However, WO 01/11011 clearly teaches that positive and negative selection techniques using antibodies are known to those of skill in the art and that the techniques for mammalian cell separation and enrichment from the mixtures of cells that are based on magnetic separation, immunoaffinity, fluorescence activated cell sorting have been described in the art (page 23, lines 13-20).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to apply the known techniques of cell sorting and enrichment to obtain 91% pure cell population of cells expressing CD90 and CD49 markers from the bone marrow mesenchymal stem cells with a reasonable expectation of success because the bone marrow mesenchymal stem cell population contains cells expressing CD49 and CD90 markers and, thus, the bone marrow mixed cell populations is a reasonable source of the required cell product. The bone marrow mesenchymal stem cells are proliferating cells and, thus, the initial amounts of cells can be expanded by culturing in order to obtain the required amounts of the final product. One of skill in the art would have been motivated to obtain a specific pure cell population including that expressing CD49 and CD90 for the expected benefit in collecting cell surface adhesion molecules and in maximizing yields of the collected amounts. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented by the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Claims 14, 19-21, 23 25 and 26 as amended are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 2002/0168765, WO 01/34167 and WO 01/11011 in the light of evidence by US 5,837,539 and Colter et al. {IDS –AW} as applied to claims 14, 19, 20, 23, 24 and 26 above, and further in view of the references by Christian van den Bos et al. and Gartel et al.

Claims 14, 19, 20, 23, 24 and 26 as explained above. Claim 21 is further drawn to the cells characterized by specific amounts of p21 and p53 transcripts.

The cited references US 2002/0168765, WO 01/34167, WO 01/11011, US 5,837,539 and Colter et al. are lacking particular disclosure related to the amounts of the p21 and the p53 transcripts in the cell populations of the mesenchymal stem cells.

However, the reference by Christian van den Bos et al. teaches that human mesenchymal stem cells from bone marrow express p21 and that the particular amounts are related to specific culture conditions, for example: cell density during culturing and/or cell commitment for differentiation. The reference by Gartel et al. is relied upon to demonstrate that the expression of p21 and p53 are related events in the cell cycle progression (page 281).

Therefore, although the bone marrow derived cell populations of the cited US 2002/0168765, WO 01/34167 and WO 01/11011 as disclosed might not be identical to the presently claimed cell population with regard to the expression and amounts of p21 and p53 transcripts, the differences between that are disclosed and that are claimed are considered to be so slight that the referenced cell populations are likely to possess the same characteristics of the claimed cell population particularly in view of the similar characteristics which they have been shown to share as explained above. Thus, the claimed cell population would have been obvious

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to those of ordinary skill in the art within the meaning of USC 103. Therefore, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

With regard to the expression of p21 and p53 it appears that the claimed invention either (i) does not require any expression of p21 and p53 (from zero to 20000 or from zero to up to 3000 as claimed) or (ii) the claimed ranges are so broad that they encompass all type of culture conditions (regular or oxidative) and all types of cell multipotentiality (undifferentiated, differentiated, proliferating, arrested) since the critical amounts/conditions which are disclosed (specification page 32, lines 11-18) fall within the claimed ranges. Thus, the meaning of the claimed ranges allow for any at all amounts of p21 and p53 as related to the functional expression of stem cell multipotentiality and/or progression through the cell differentiation as encompassed by claims 19 and 20.

### ***Response to Arguments***

Applicants' arguments filed 12/24/2003 have been fully considered but they are not all found persuasive.

Claim rejections under 35 U.S.C. 102 have been withdrawn as explained above.

Main applicants' argument is directed to the idea that the culture conditions for providing cell populations as disclosed by the cited patents are different from the instant invention because the cited patents US 2002/0168765, WO 01/34167 and WO 01/11011, encompass the use of oxygen at about atmospheric amounts (in view of the Exhibit A-G references) but the cells of the instant invention are provided under low oxygen conditions.



In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "low oxygen" cell culture conditions or the use of 5% oxygen-containing gas mixture for proving the claimed product) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Moreover, the final applicants' product appears to be a cell population committed to a nervous system cell lineage as disclosed (examples 7 and 8) and as argued (response page 17). Yet, the claimed invention encompasses differentiation of cells towards various cell lineages including osteoclasts, muscles, pancreatic islets, hepatocytes (claims 19 and 20) that are reasonably expected to be provided under various and specific culture conditions.

Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references.

No claims are allowed.

#### ***Information Disclosure Statement***

All the information disclosure statements and/or copies of the IDS that were within 09/960,244 and that are presently within the IFW 09/960,244 have been considered by examiner. The 1449 form(s) filed with the last response (12/24/2003) are attached herein. All the IFW copies of the 1449 form(s) filed earlier by applicants are provided herein for the applicants' convenience.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at (571) 272-0926.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Vera Afremova

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March 19, 2004



VERA AFREMOVA

PATENT EXAMINER